Government Chemist Conference 21-22 June 2016, London

Antimicrobial resistance and the food chain

Paul Cook

Microbiological Risk Assessment

Science, Evidence & Research Division

Paul.Cook@foodstandards.gsi.gov.uk

Food Standards Agency
food.gov.uk

Outline of presentation

- What is antimicrobial resistance?
- The UK and international dimension
- Role of the food chain
- Systematic review
- Surveillance
- Looking ahead

Food Standards Agency
food.gov.uk

Antimicrobials and resistance

- A compound which, at low concentrations, exerts an action against microorganisms and exhibits selective toxicity towards them
- Any substance of natural, synthetic or semisynthetic origin which is used to kill or inhibit the growth or microorganisms- bacteria, fungi, protozoa, viruses
- Antimicrobials include antibiotics, disinfectants, preservatives, other substances (e.g. copper, zinc)
- Antimicrobial resistance is the ability of a microorganism to withstand an antimicrobial

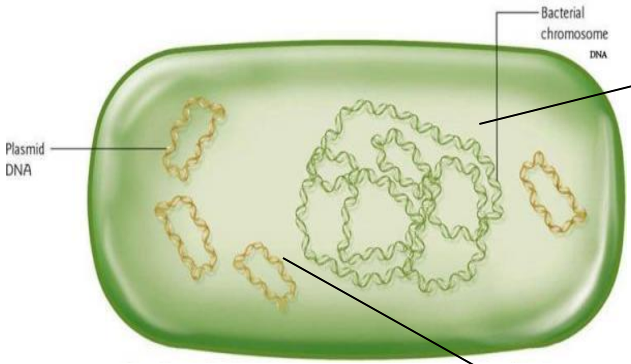
Source: ACMSF (1999)

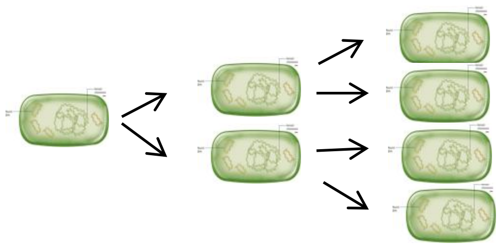
Food Standards Agency
food.gov.uk

What is antimicrobial resistance?

- Can arise randomly - mutation in any gene occurs in ~1 cell per 10 million
- Mutants which give rise to resistance are selected - sensitive cells are killed

How does resistance transfer?

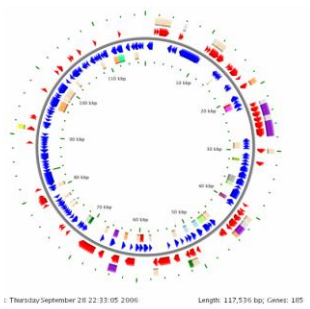


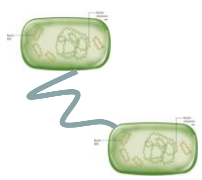


Chromosomal - only to daughter Cells- vertical

VERTICAL TRANSMISSION

Transferable – between bacteria
Elements within plasmids - transposons and integrons





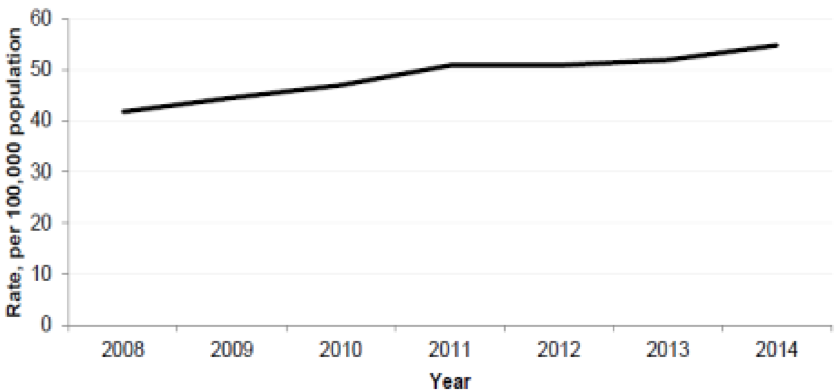
HORIZONTAL TRANSMISSION

Pathogen ⟷ Commensal

Pathogen or commensal?

- Impact can be direct or indirect (silent)
- Pathogens such as *Salmonella*, *Campylobacter* and *E.coli* O157 cause infectious intestinal disease (IID) and some strains will carry antimicrobial resistance genes which may be transferable to other bacteria.
- IID is usually self-limiting with antibiotics only being required if the infection becomes more serious.
- Other bacteria (e.g. commensal *E.coli* and *Klebsiella)* may or may not not cause infection but can carry antimicrobial resistance genes transferable to other bacteria some of which may cause disease at some point.
- More work is needed to understand the role of the human gut microbiome as a reservoir for drug resistance genes.

Figure 1. ***E. coli*** **bacteraemia rates per 100,000 population (England, Wales, and Northern Ireland): 2008-2014***



* Data extracted on 14 April 2015

PHE data - English surveillance Programme for antimicrobial utilisation and resistance (ESPAUR) 2010 to 2014*

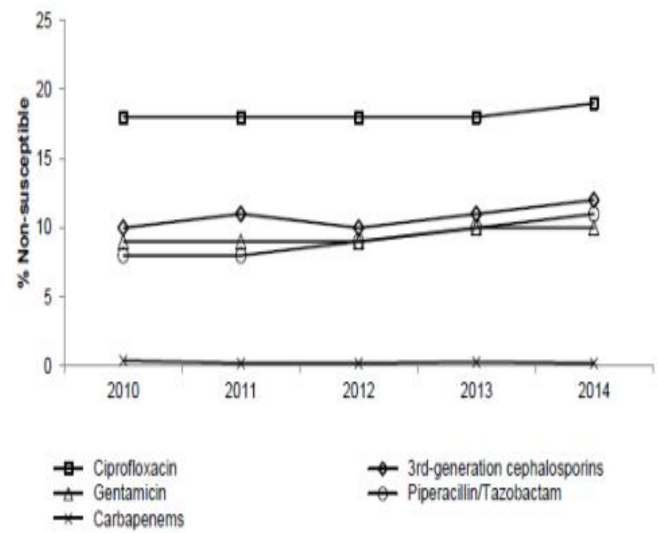


Figure 2.2 Proportions of bloodstream isolates of *E. coli* non-susceptible to indicated antibiotics, England, 2010–2014

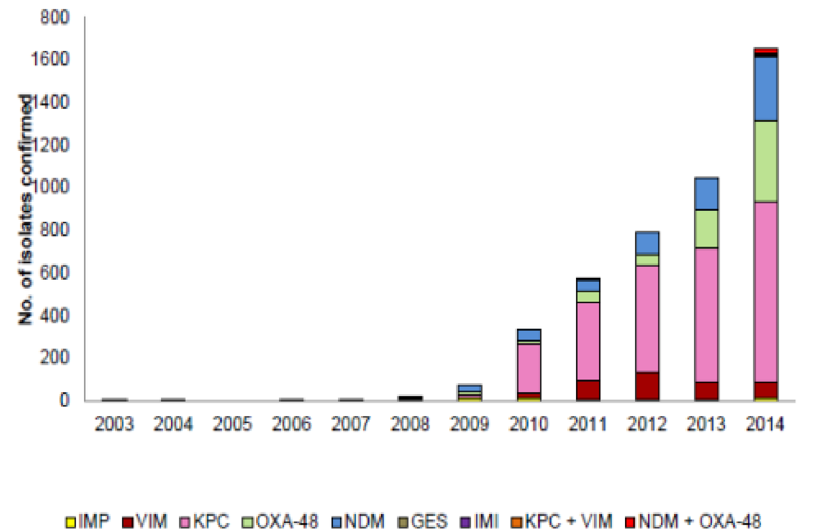
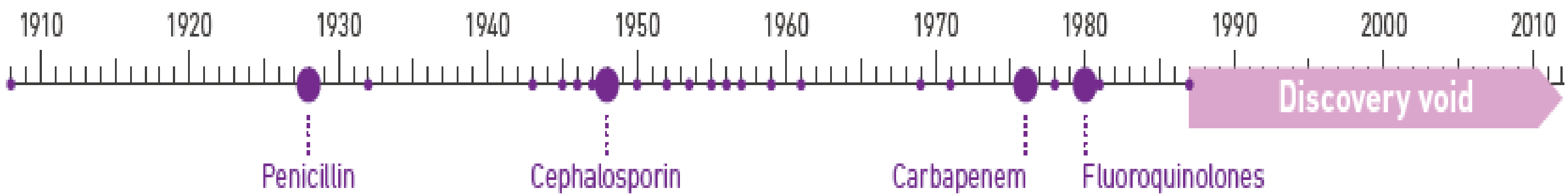


Figure 2.10 Number of isolates referred from UK hospital microbiology laboratories confirmed as carbapenemase-producing Enterobacteriaceae by AMRHAI, 2003–2014

*Source: Public Health England https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477962/ESPAUR_Report_2015.pdf

The antibiotic timeline

Over the last 30 years, no major new types of antibiotics have been developed



Resistance can arise soon after new antimicrobial drugs are introduced

Penicillin, B lactams - discovered 1928, introduced 1938, resistance 1945
Macrolides, erythromycin – discovered 1948, introduced 1951, resistance 1955
Quinolones – discovered 1961, introduced 1968, resistance observed 1968

“Human use of antibiotics has selected for the escape of genes from the soil ‘resistome’ into human pathogens, as demonstrated by the presence of the same genes in soil bacteria and human bacteria” Blair *et al*. (2015)

What does this mean?

Without urgent action we are heading for a post-antibiotic era, in which common infections and minor injuries can once again kill

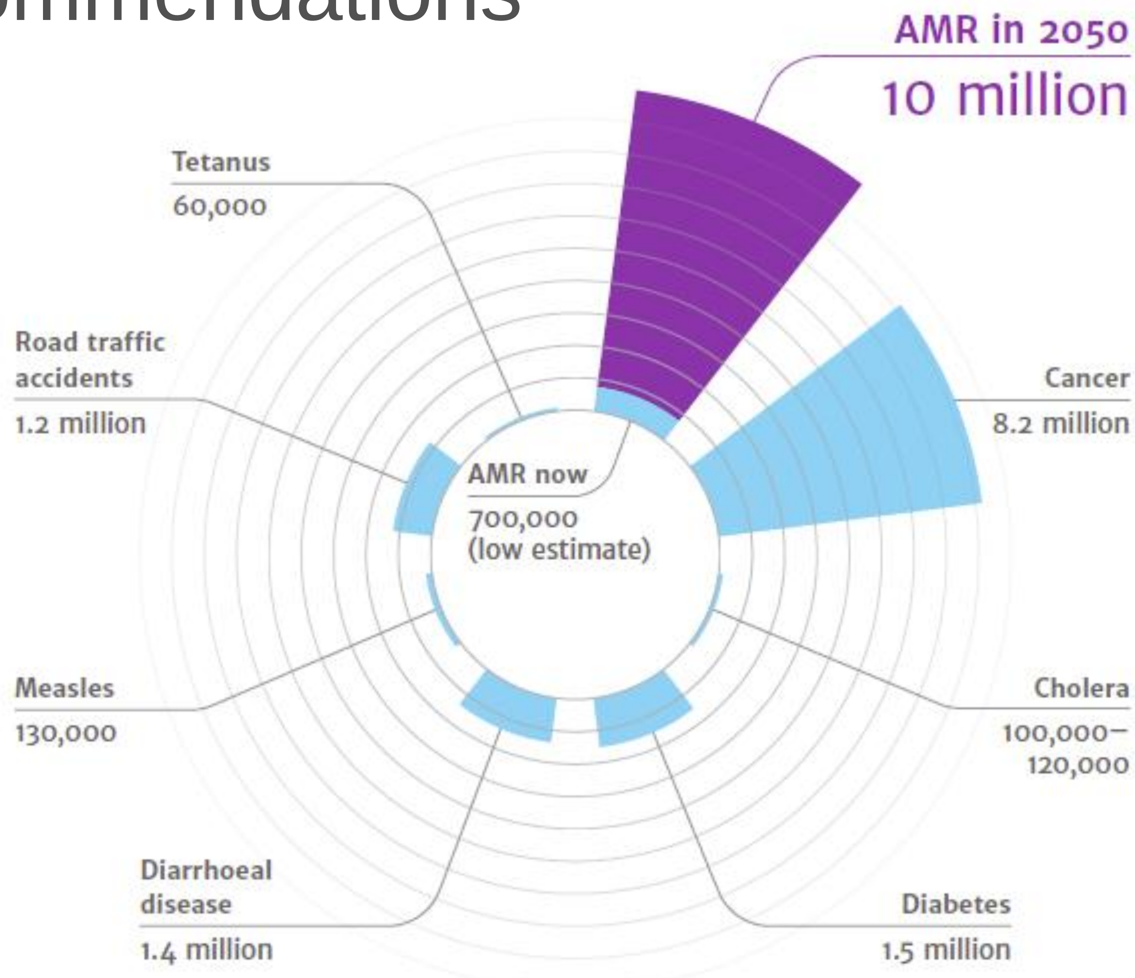
Sources: WHO Antimicrobial resistance Global Report on surveillance 2014; Blair et al., Nature Reviews **13** (2015); Lewis (2013) Nature Reviews Drug Discovery **12**:371–387

O’Neill Review - tackling drug-resistant infections globally; final report and recommendations

- 2016 – 700,000 deaths per year
- 2050 - 10,000,000 deaths per year

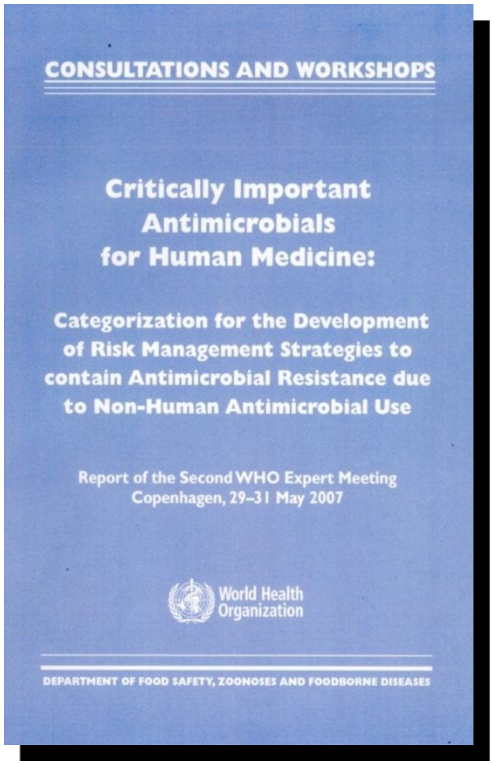
Cost $100 trillion on global world GDP

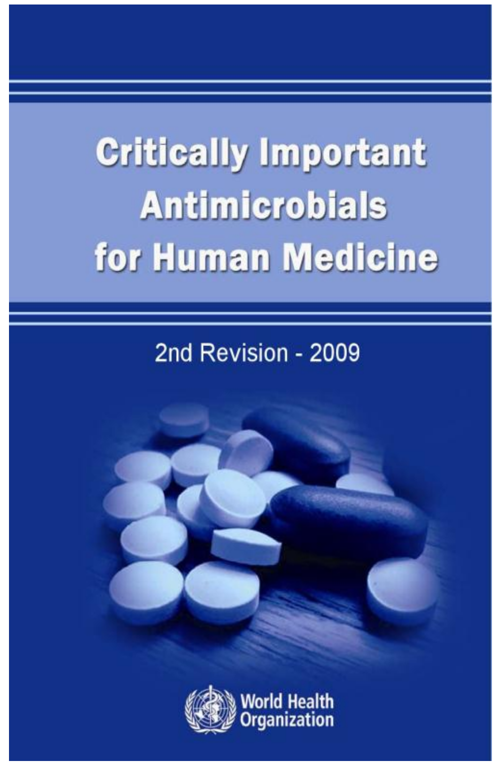
Review on Antimicrobial Resistance
Tackling drug-resistant infections globally

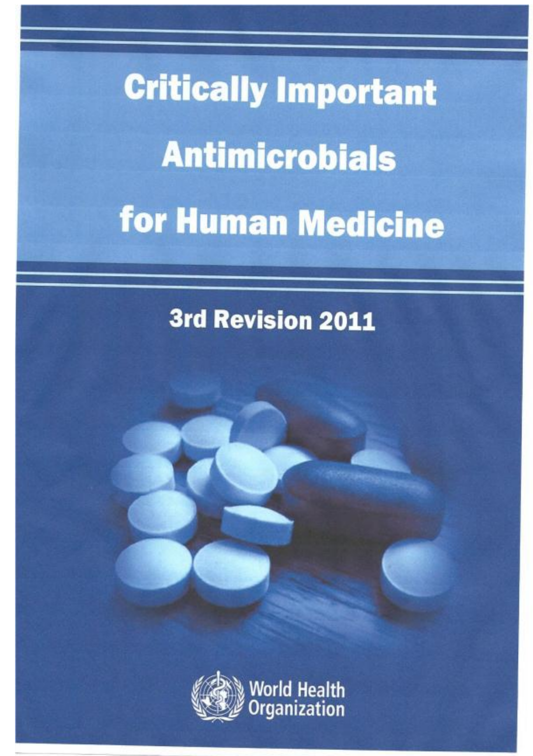


Source: Tackling drug-resistant infections globally; final report and recommendations. The Review on AMR chaired by Jim O’Neill, May 2016

Critically-Important Antimicrobials (CIAs)
WHO, 2007, 2009, 2011







e.g. Quinolones / fluoroquinolones
3rd / 4th generation cephalosporins
Carbapenems

OIE List of Antimicrobials of Veterinary Importance

OIE LIST OF ANTIMICROBIALS OF VETERINARY IMPORTANCE

Criteria used for categorisation | List of antimicrobials

The OIE International Committee unanimously adopted the List of Antimicrobials of Veterinary Importance at its 75th General Session in May 2007 (Resolution No. XXVIII).

Background

Antimicrobial agents are essential drugs for human and animal health and welfare. Antimicrobial resistance is a global public and animal health concern that is influenced by both human and non-human antimicrobial usage. The human, animal and plant sectors have a shared responsibility to prevent or minimise antimicrobial resistance selection pressures on both human and non-human pathogens.

The FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance held in Geneva, Switzerland, in December 2003 (Scientific Assessment) and in Oslo, Norway, in March 2004 (Management Options) recommended that the OIE should develop a list of critically important antimicrobials in veterinary medicine and that WHO should also develop such a list of critically important antimicrobials in human medicine.

Conclusion No. 5 of the Oslo Workshop is as follows:

5. The concept of "critically important" classes of antimicrobials for humans should be pursued by WHO. The Workshop concluded that antimicrobials that are critically important in veterinary medicine should be identified, to complement the identification of such antimicrobials used in human medicine. Criteria for identification of these antimicrobials of critical importance in animals should be established and listed by OIE. The overlap of critical lists for human and veterinary medicine can provide further information, allowing an appropriate balance to be struck between animal health needs and public health considerations.

Responding to this recommendation, the OIE decided to address this task through its existing ad hoc Group on antimicrobial resistance. The terms of reference, aim of the list and methodology were discussed by the ad hoc Group since November 2004 which was subsequently endorsed by the Biological Standards Commission in its January 2005 meeting and adopted by the International Committee in May 2005. Thus, the work was officially undertaken by the OIE.

Preparation of the draft list

The Director General of the OIE sent a questionnaire prepared by the ad hoc Group accompanied by his letter explaining the importance of the task to OIE Delegates of all Member Countries and international organisations having signed a Co-operation Agreement with the OIE in August 2005.

Sixty-six replies were received. This response rate highlights the importance given by OIE Member Countries from all regions to this issue. These replies were analyzed first by the OIE Collaborating Centre for Veterinary Dugs, then discussed by the ad hoc Group at its meeting in February 2006. A list of proposed VCIA was compiled together with an executive summary. This list was endorsed by the Biological Standards Commission and circulated among Member Countries aiming for adoption by the OIE International Committee during the General Session in May 2006.

Discussion at the 74th International Committee in May 2006

The list was submitted to the 74th International Committee where active discussion was made among Member Countries. Concerns raised by Member Countries include: 1) the list includes substances that are banned in some countries; 2) some of the substances on the list are not considered "critical"; 3) nature of the list – is this mandatory for Member Countries?; and 4) the use of antimicrobials as growth hormone is included. While many Member Countries appreciated the work, it was considered appropriate to continue refinement of the list. The list was adopted as a preliminary list by Resolution No. XXXIII.

Refinement of the list

The *ad hoc* Group was convened in September 2006 to review the comments made at the 74th General Session of the OIE International Committee, and Resolution No.XXXIII adopted at the 74th General Session. Based on the further analysis provided by the OIE Collaborating Centre for Veterinary Medicinal Products, the *ad hoc* Group prepared its final recommendations of the list of antimicrobials of veterinary importance together with an executive summary. Once again, this was examined and endorsed by the Biological Standards Commission in its January 2007 meeting and circulated among member Countries.

Adoption of List of Antimicrobials of Veterinary Importance

The refined list was submitted to the 75th International Committee during the General Session in May 2007 and adopted unanimously by Resolution No. XXVIII.

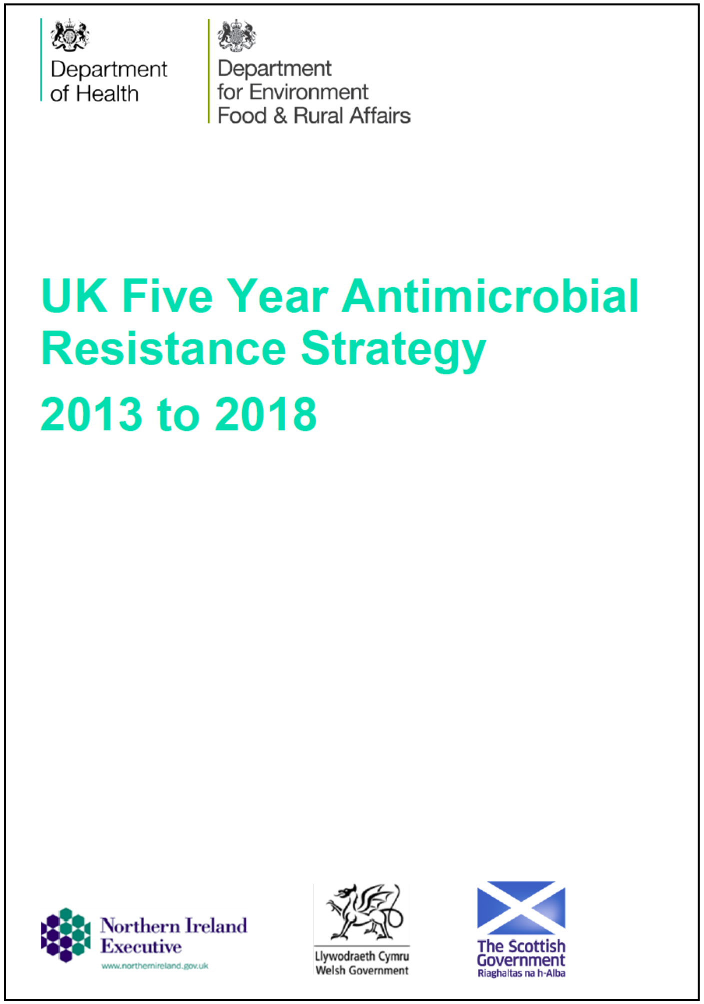
Defines:

- Veterinary Critically Important Antimicrobials
- Veterinary Highly Important Antimicrobials
- Veterinary Important Antimicrobials:

'Critically Important' include

- Aminoglycosides
- Cephalosporins
- Macrolides
- Quinolones/ fluoroquinolones

UK AMR Strategy


Department of Health

Department for Environment Food & Rural Affairs

UK Five Year Antimicrobial Resistance Strategy

2013 to 2018

Northern Ireland Executive

www.northernireland.gov.uk

Llywodraeth Cymru Welsh Government

The Scottish Government Riaghaltas na h-Alba

The overall goal of the cross-government UK strategy is to slow the development and spread of antimicrobial resistance by focusing activities around 3 strategic aims:

- improve the knowledge and understanding of antimicrobial resistance
- conserve and steward the effectiveness of existing treatments
- stimulate the development of new antibiotics, diagnostics and novel therapies

FSA involved with the strategy and delivery of the action plan

Food Standards Agency
food.gov.uk

FSA STRATEGIC OUTCOMES

- Food is safe
- Food is what it says it is
- Consumers can make informed choices about what to eat
- Consumers have access to an affordable healthy diet, now and in the future

Food Standards Agency
food.gov.uk

Antimicrobial resistance and food

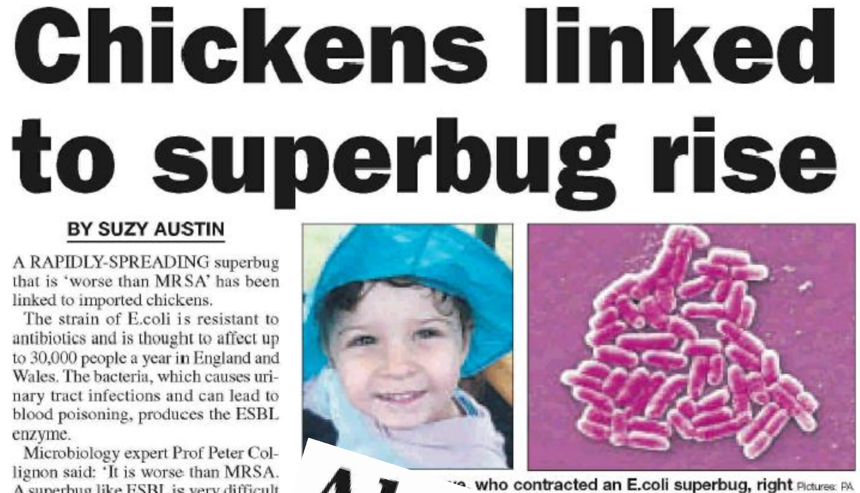
New E.coli strain 'more dangerous than MRSA'

Daily Mail Reporter

A STRAIN of E.coli linked to imported meat is spreading rapidly throughout England and Wales and now affects around 30,000 people a year, an investigation has revealed.

ducer then we run out of options of how to treat them. It looms like an emerging plant. Basically it's

Resistant E.coli 'linked to imported meat' spreading



Chickens linked to superbug rise

BY SUZY AUSTIN

A RAPIDLY-SPREADING superbug that is 'worse than MRSA' has been linked to imported chickens.

The strain of E.coli is resistant to antibiotics and is thought to affect up to 30,000 people a year in England and Wales. The bacteria, which causes urinary tract infections and can lead to blood poisoning, produces the ESBL enzyme.

Microbiology expert Prof Peter Collignon said: 'It is worse than MRSA. A superbug like ESBL is very difficult

... who contracted an E.coli superbug, right Pictures: PA

Alert over food superbug that kills 3,000 a year

By Mark Reynolds

A SUPERBUG deadlier than MRSA and mad cow disease is killing 3,000 people a year – but most GPs have never heard of it.

But an investigation by ITV's Tonight With Trevor McDonald programme found that 70 per cent of family doctors were totally unaware of it.

Frighteningly, it is now spreading but is difficult to detect. Only one type of antibiotic can treat it reli-

FSA Online Omnibus survey 1263 adults May 2016

74% had heard of "superbugs" (highest among those aged 55+) ;

61% had heard of antibiotic resistance;

16% had heard of antimicrobial resistance.

Of those aware of any of those terms 62% were concerned about AM/AB resistance within the food chain.

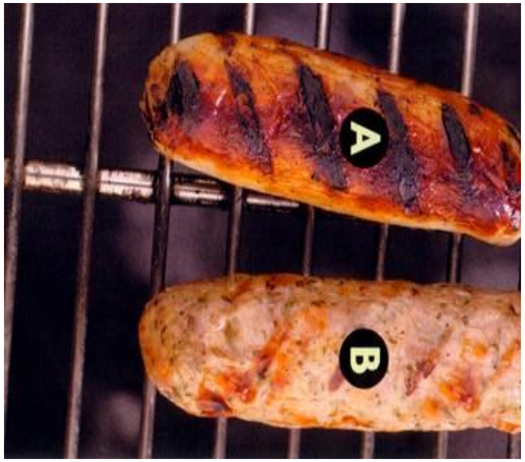
Washing hands regularly

4 Cs

Chilling food properly

Cooking food properly

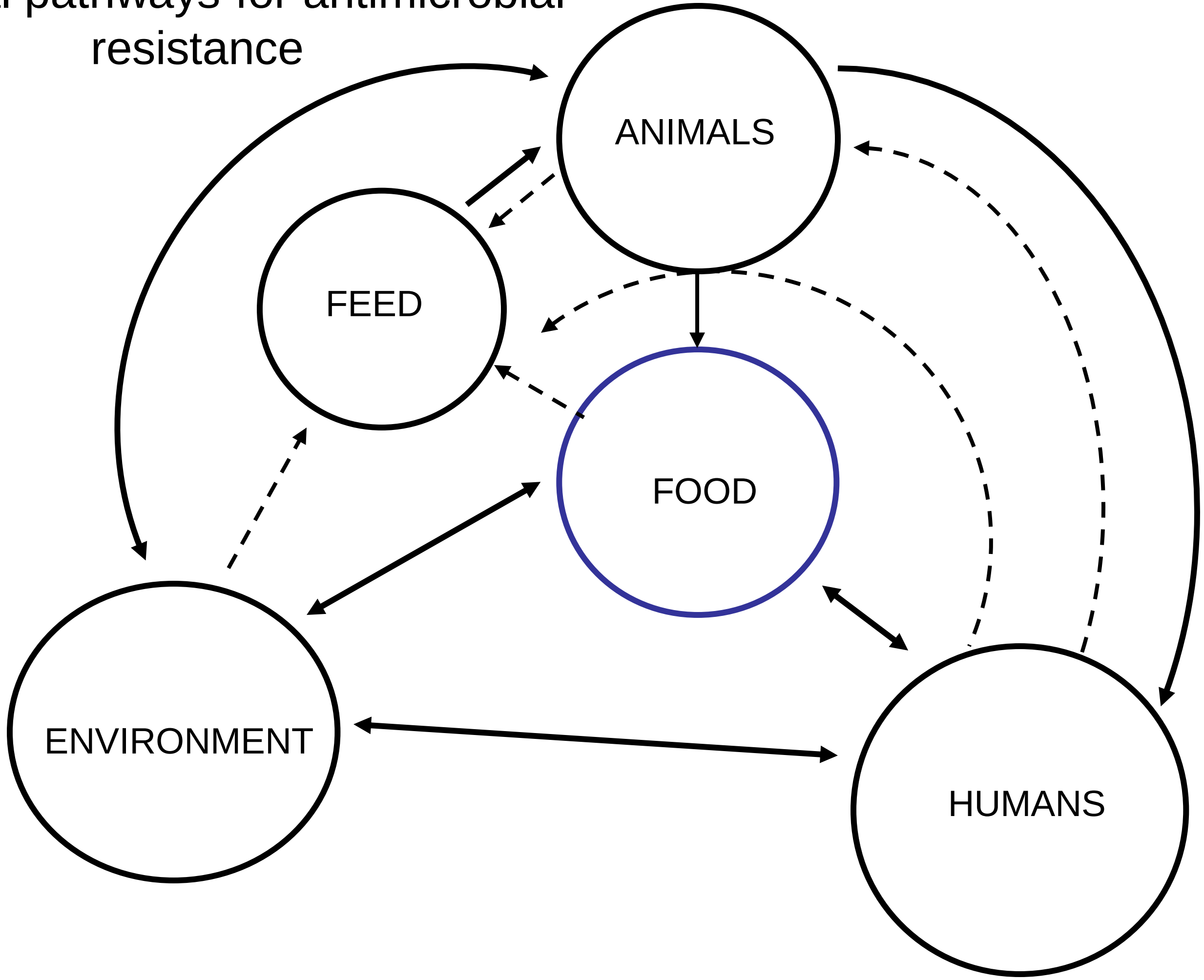
Avoiding cross contamination



Antimicrobial resistant bacteria are no more heat resistant

Food Standards Agency
food.gov.uk

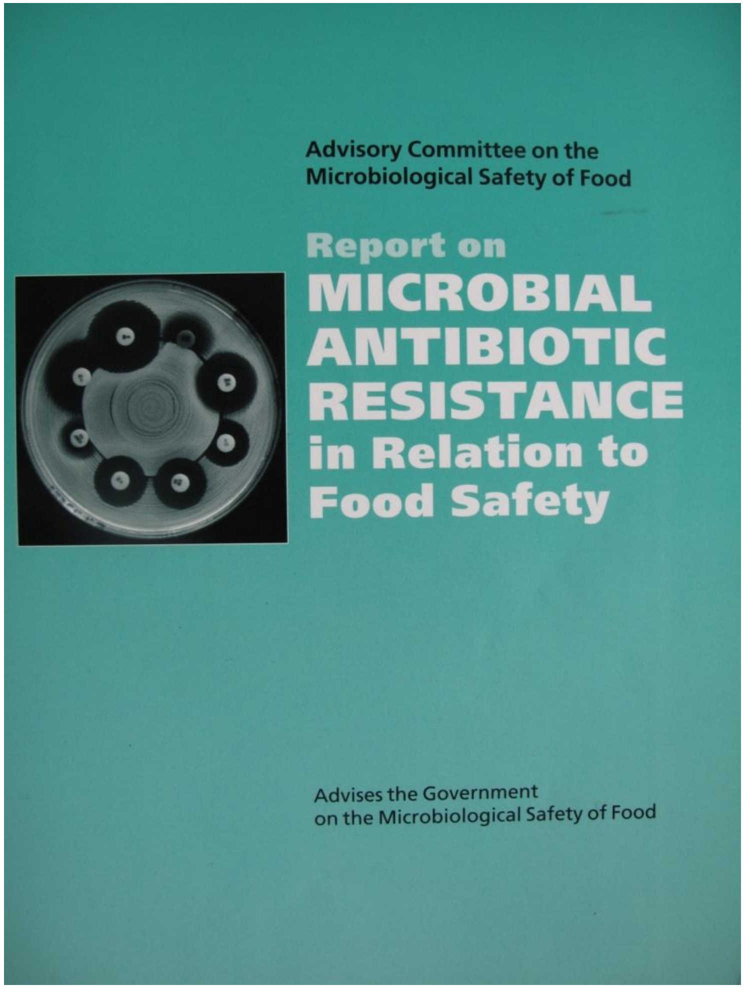
Potential pathways for antimicrobial resistance



Source: ACMSF (1999) Microbial Antibiotic Resistance in Relation to Food Safety, HMSO

Food Standards Agency
food.gov.uk

1999 - Advisory Committee on the Microbiological Safety of Food (ACMSF)



Some evidence of transmission via the food chain- *Salmonella*, *Campylobacter*

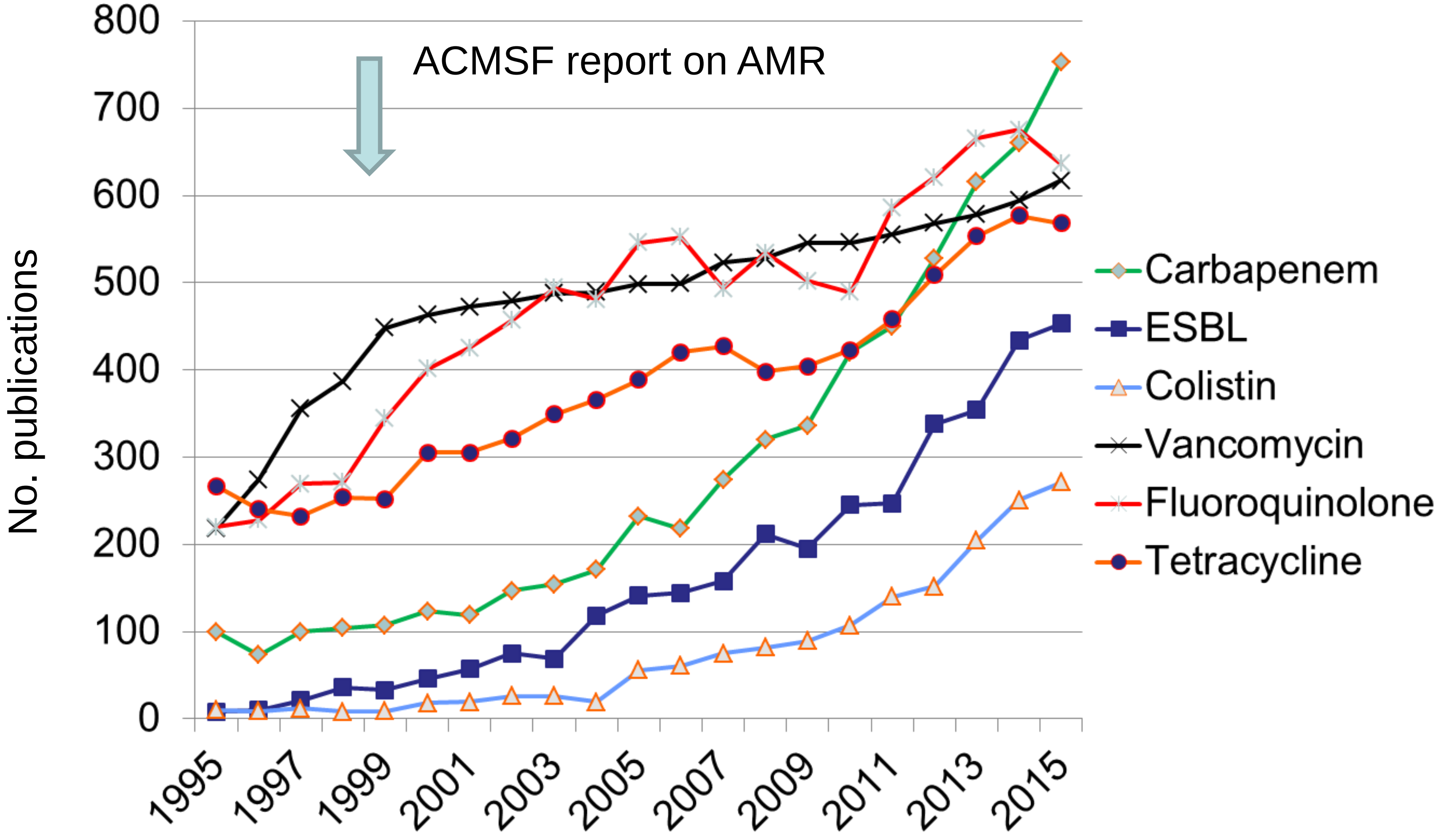
Paucity of food data and collected for different purposes

Difficult to compare–sampling and methodology

Need for more screening of *E.coli* isolates from foodstuffs

Food Standards Agency
food.gov.uk

Growth in the literature on antimicrobial resistance - selected traits -1995-2015



Source: PubMed search accessed 20 June 2016

Growth in the scientific literature on antimicrobial resistance to June 2016- all aspects and selected resistance traits

Resistance trait	Antimicrobial Resistance	Antimicrobial resistance + food	%
All aspects	185,772	9,399	5.1%
Carbapenem	6,888	105	1.5%
ESBL	3,619	255	7.0%
Colistin	2,243	102	4.5%
Fluoroquinolone	11,725	637	5.4%
Vancomycin	11,756	713	6.1%
Tetracycline	10,827	1,492	13.8%

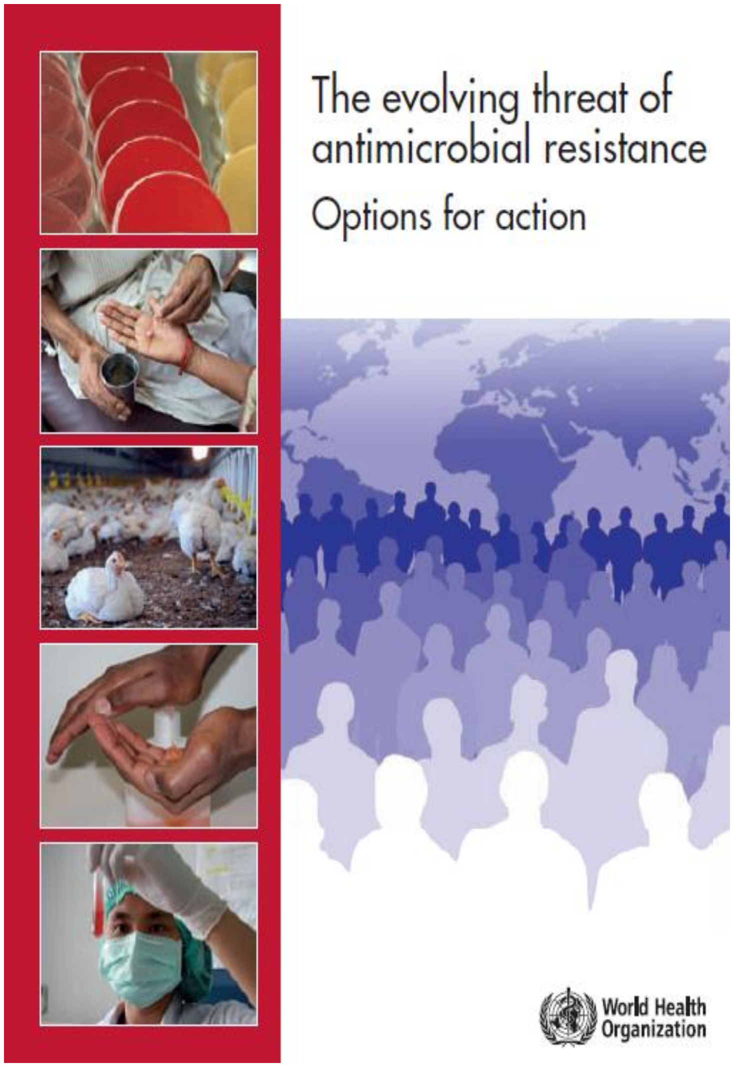
Source: PubMed - accessed 20 June 2016

Evidence gathering – Royal Veterinary College Systematic Review on AMR

- A systematic literature review of the occurrence of antimicrobial resistance in pathogens and commensals in retail food
- Focus on *Salmonella*, *Campylobacter*, *E.coli* and Enterococci
- Critically important antimicrobial groups and multi-drug resistance
- Follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
- PROSPERO an international database of prospectively registered systematic reviews
- Studies published between 1999-2015 (since the last ACMSF report)
- Peer reviewed literature and some "grey literature"
- Publication expected September 2016
- Gaps in review will help to guide future research

http://www.prisma-statement.org/Default.aspx

The evolving threat of antimicrobial resistance



WHO report (2012) Chapter 4: Reducing the use of antibiotics in animal husbandry

"More information is needed on the prevalence of AMR in bacteria of animal origin and its impact on human health, on the quantity of antibiotics used for different indications and on the classes of antibiotics used".

"Risk assessments and risk management are impeded by a lack of data and/or inability to access available data"

CODEX has produced guidelines for risk analysis of foodborne antimicrobial resistance CAC/GL77-2011

http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf

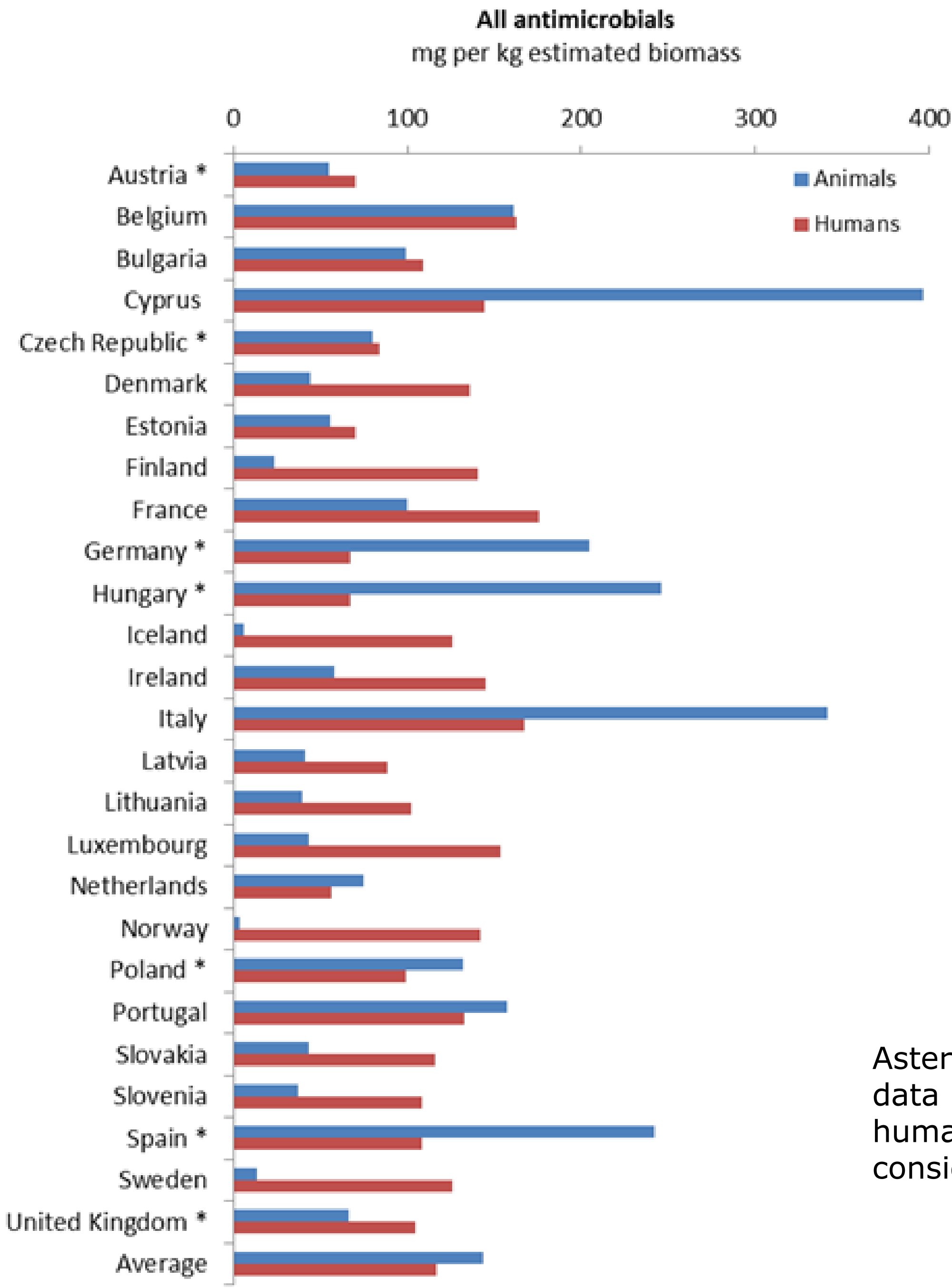
JIACRA - Joint Inter-agency Antimicrobial Consumption and Resistance Analysis

- First integrated report by the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA)

- "The epidemiology of resistance is complex, and several factors aside from the amount of antimicrobial consumption influence the level of resistance"

- "No associations were observed between the consumption of fluoroquinolones in food-producing animals and the occurrence of resistance in *Salmonella* spp. and *Campylobacter* spp. from cases of human infection".

http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-JIACRA-report.pdf
Report published January 2015

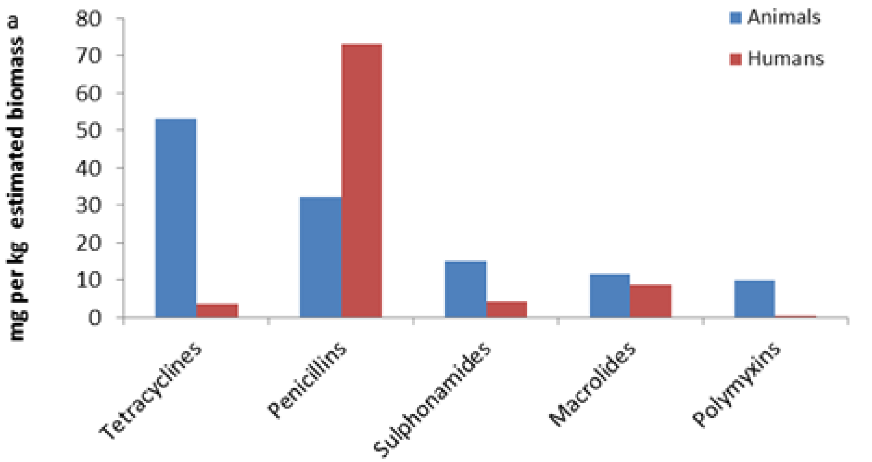


Comparison of biomass-corrected consumption of antimicrobials (mg per kg estimated biomass) in humans and animals in 26 EU/EEA countries in 2012

Asterisk (*) denotes that only community consumption data were available for human medicine. Figures of human sales from these countries probably represent a considerable underestimate.

nt Interagency Antimicrobial Consumption and Resistance Analysis

Comparison of consumption of selected antimicrobial classes for humans and food-producing animals in 26 EU/EEA countries in 2012



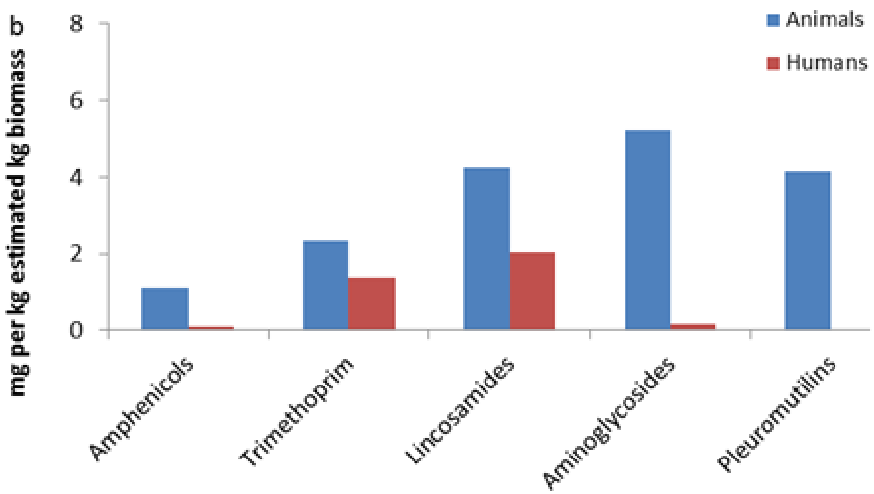
Highest selling AMs classes:

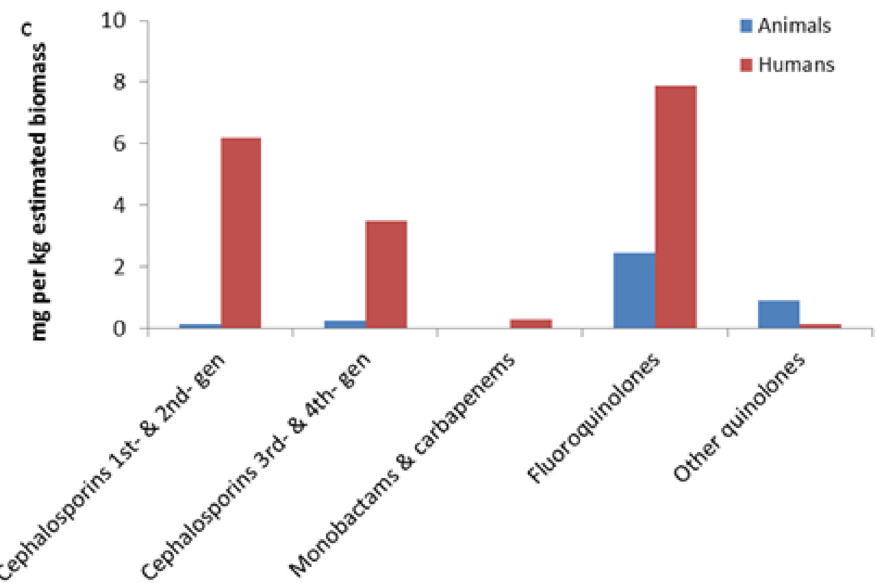
- Human medicine:

penicillins, macrolides, fluoroquinolones

- Food-producing animals:

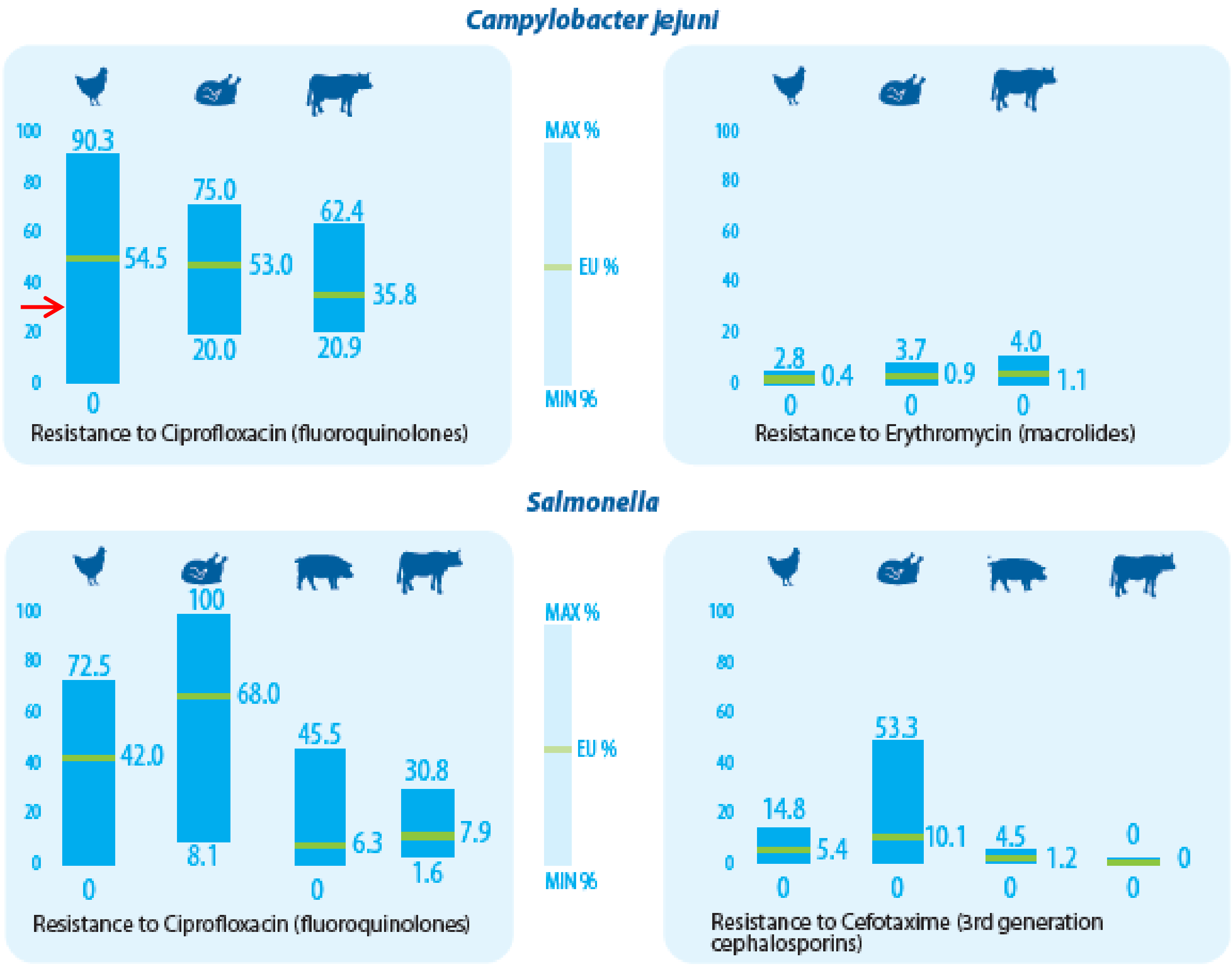
tetracyclines, penicillins, sulphonamides





Source: JIACRA

Levels of AMR in the Food Chain



Variability in percentage of bacteria presenting microbiological resistance reported by Member States

Based on “European Union Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013”.

Source: EFSA

Food Standards Agency
food.gov.uk

http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-zoonotic-bacteria-humans-animals-food-EU-summary-report-2013.pdf

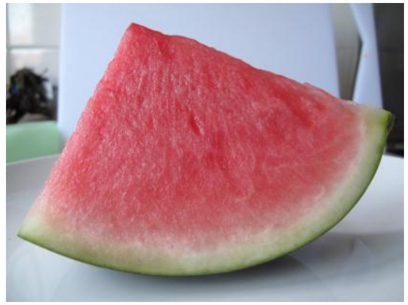
Need for better alignment of AMR data

- EU surveillance (Decision 2013/652/EC)
- Lays down specific technical requirements for AMR testing and reporting in representative isolates from randomised sampling of food animals at farm and/or slaughter, and retail meat
- Testing stated in 2015-2020 for retail meat in all 28 Member States
- Testing retail meats (beef/pork/chicken) in the UK for: ESBL-/ AmpC-/ Carbapenemase-producing *E. coli)*
- FSA included testing for colistin resistance and the *mcr-1* colistin resistance gene
- EU results for 2015 expected in early 2017

Food Standards Agency
food.gov.uk

.

Antimicrobial resistance and fresh produce?

- Global sourcing of a diverse range of fresh produce -minimal processing

- Shiga toxin producing *E.coli* O104:H4 outbreak in 2011 - ~4000 EHEC cases, >900 HUS cases, 54 deaths. Linked to Fenugreek seeds from Egypt. Strain resistant to a wide range of β-lactamase antibiotics (ESBL), streptomycin, nalidixic acid, tetracyclines, trimethoprim sulphonamides
- (Bielaszewska et al., 2011)

- EFSA reports some information - need for more studies

- FSA are supporting a collaborative study with DH to quantify ESBL-producing *E. coli* in raw meats and fresh produce

Food Standards Agency
food.gov.uk

AMR - Plasmid-mediated colistin resistance (*mcr-1* gene) – Nov 2015

- Plasmid-mediated colistin resistance reported from *E.coli* in pigs, raw meat and human infections in China*
- Resistance previously thought to be chromosomal
- Now becoming an antibiotic of last resort for certain infections in human medicine
- Animal and Plant Health Agency find *mcr-1* gene in *E.coli* in UK pigs.
- Public Health England screened WGS archive of 24,000 bacterial isolates for *mcr-1* gene (24 hours) – found 12 *Salmonella* and 3 *E.coli* isolates with *mcr-1*
- Denmark (DTU) reported 6 positives from screening ~3000 WGS

*Liu et al. (2015) *The Lancet infectious Diseases* 16: 161-168

Food Standards Agency
food.gov.uk

AMR - Plasmid-mediated colistin resistance (*mcr-1* gene)

- In China 0.7-1.4% of inpatient isolates of *E.coli* and *Klebsiella pneumoniae* with the *mcr-1* gene - much lower than in animals (21%) or pork, chicken (15%).
- Frequency of *mcr-1* gene in UK clinical isolates ~10 fold lower
- UK direct and indirect risk was very low - medium to high uncertainty - supported by ACMSF
- Jan 16 - screening of *E.coli* from retail meat for the *mcr-1* gene as an add on to EU antimicrobial resistance monitoring - more data needed!
- *mcr-1* gene now reported from many countries
- EU AMEG re-looked at colistin – report May 16

Food Standards Agency
food.gov.uk

Looking ahead

- FSA Board – paper on antimicrobial resistance
- RVC systematic review
- Risk assessment for Meticillin-resistant *Staphylococcus aureus* (MRSA) in the food chain
- Antimicrobial resistance in *Campylobacter* from retail chicken
- 2015 findings from EU surveillance of animals and retail meats
- Joint EFSA-EMA opinion on measures to reduce the need to use antimicrobials in animal husbandry (RONAFA)

Food Standards Agency
food.gov.uk

THANK YOU

Acknowledgement: John Threlfall